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Description

This invention relates to granules of cimetidine which are useful in the preparation of tablets and which have an improved flavour.

5 Cimetidine is a histamine H₂-antagonist which has been described in U.K. Patent Specification 1,397,436. Cimetidine has been shown to be useful in the treatment of duodenal, gastric, recurrent and stomal ulceration, and reflex oesophagitis and in the management of patients who are at high risk from haemorrhage of the upper gastro-intestinal tract.

10 Cimetidine is known to have a pronounced bitter taste. This is not usually a problem when the dosage form employed is a capsule or a tablet designed to be swallowed, thereafter to disintegrate upon reaching the stomach. However, such dosage forms can be impractical when it is desired to administer a large amount of active ingredient, or to co-administer a relatively bulky second active ingredient such as an antacid or algininate. Moreover many individuals have difficulty in swallowing a solid dosage form.

15 A conventional approach to administering relatively large amounts of active ingredient in a solid dosage form is by means of a chewable tablet, i.e. a tablet which disintegrates in the mouth upon being chewed. Such a tablet also circumvents the problem of a solid dosage being difficult to swallow.

20 It will be appreciated that a major requirement of such a dosage form is that it must be palatable, since an unpalatable formulation increases the risk of a patient neglecting to take the tablet. Such non-compliance with the dosing regimen will in turn delay or prevent the patient's recovery from the condition under treatment.

A further requirement of such a composition is that once the disintegrated tablet reaches the stomach, the individual particles should release the active ingredient rapidly and completely in order to ensure that substantially all of the active ingredient is absorbed; that is to say the formulation should be bioavailable.

25 In the case of cimetidine, because of its bitterness, the provision of such a dosage form represents a considerable problem.

Several solutions to this problem have been proposed. One proposal is disclosed in Japanese Patent Application No. 67375/80 wherein there are described granules of cimetidine containing ethylcellulose preferably in the range of 15 to 85% (w/w) and particularly preferably 50% (w/w) relative to the cimetidine. Such granules are described as having good stability to light, good dissolution characteristics and are 30 stated not to have a bitter taste. These properties are stated to be specific to granules containing ethylcellulose; it is disclosed that methylcellulose does not impart such properties.

Another proposed solution is disclosed in Japanese Patent Application No. 86228/78 which similarly describes cimetidine granules containing a polymeric substance; in this case specifically polyvinylacetal diethylamino-acetate.

35 One general approach to the masking of the taste of bitter medicaments has been to coat the medicament with a waxy, fatty or oily substance.

Thus, for example, British Patent No. 2,081,092 discloses the use of waxy substances to mask the bitter taste of certain medicaments. Particular waxy substances mentioned are carnauba wax, beeswax, solid fats and oils such as castor wax, acetoglyceride, higher fatty acids such as stearic acid, palmitic acid and higher 40 alcohols such as cetyl alcohol and stearyl alcohol. However, GB 2,081,092 also discloses that, in order to avoid the known problem of the waxy substance retarding the dissolution and absorption of the active ingredient, it is necessary also to include in the formulation a water-swellable high molecular weight material such as cross-linked polyvinylpyrrolidone.

45 Fats and oils are composed mainly of triglycerides, i.e. glycerol in which all three hydroxyl groups have been esterified with fatty acids. In the pharmaceutical field, such triglycerides are used mainly as suppository bases or as constituents of ointments and creams.

Partially hydrolysed glycerides such as mono- and di-glycerides are also known to be used in the preparation of pharmaceutical compositions but these are in general employed as emulsifiers and emulsion stabilisers, for example in oil-in-water and water-in-oil emulsions.

50 A further known use of glycerol esters is as releaseretarding coatings in sustained release formulations. For example, British Patent Application GB 2,119,247A discloses a sustained release tablet of lithium carbonate in which the release-retarding agent is a mixture of glyceryl mono-, di- and tri-esters of one or more straight chain fatty acids. The sustained release formulations disclosed in GB 2,119,247A optionally contain a surfactant such as sodium lauryl sulphate.

55 US-A-3308217 discloses thermoplastic materials such as glycerol esters as granulating agents.

Surprisingly, we have now found that a cimetidine granule which has good palatability but also has good dissolution characteristics can be prepared by granulating the cimetidine with a glycerol or sucrose ester wherein at least one hydroxyl group has been esterified with a C₆₋₂₄ fatty acid, particularly a C₁₂₋₂₄

fatty acid such as stearic acid or palmitic acid. Such granules need not contain a water-swellaable high molecular weight substance of the type disclosed in GB 2,081,092.

Particular esters are mixtures of monoesters and/or diesters and/or triesters or substantially pure monoesters and diesters.

5 The type and quantity of the esters employed in the granules of the present invention is selected such that the bitter taste of the cimetidine is masked and preferably such that the granules have dissolution characteristics whereby 90% by weight of the cimetidine in a granule dissolves within 50 minutes as measured using the US Pharmacopoeia Paddle test (paddle speed 100 r.p.m.)(USP XXI, pp.1243-1244).

10 The glycerol ester or sucrose ester, is usually present in an amount corresponding to at least 15% and suitably from 15% to 100% by weight relative to the cimetidine; particularly 20% when the ester is a glycerol ester.

15 The glycerol esters available commercially frequently are provided as a mixture of mono-, di- and tri-glycerides of various fatty acids. For example, commercially available glyceryl monostearate is often provided as a mixture comprising mainly glyceryl monostearate and glyceryl monopalmitate, as well as variable quantities of di- and tri-glycerides. The US Pharmacopoeia (USP XXI/NF XVI, p.1565) definition of glyceryl monostearate refers to a mixture containing not less than 90% of monoglycerides of saturated fatty acids whereas the British Pharmacopoeia (BP 1980, pp.212-213) defines glyceryl monostearate as a mixture containing not less than 35% of monoglycerides. Because glycerol esters are usually provided as mixtures, it is most convenient to define them in terms of their bulk properties and in particular their chemical reactivities towards certain standard reagents. One such property which will be used herein to define the glycerol esters of the present invention is the hydroxyl value.

20 The hydroxyl value of a glycerol ester is a measure of the number of free hydroxyl groups and is defined in the US Pharmacopoeia (USP XXI, p.1200) as the number of mg. of potassium hydroxide equivalent to the hydroxyl content of 1.0g of the substance.

25 Particular glycerol esters are those selected from:

- a) glycerol esters having a hydroxyl value of greater than 120;
- b) glycerol esters having a hydroxyl value of greater than 60 and having a triglyceride content of less than 30% by weight; and
- c) glycerol esters having a hydroxyl value of greater than 5 and a melting point of less than 40° C.

30 Examples of glycerol esters in category a) are those which are composed mainly of monoglycerides, such as glyceryl monostearate, and which have a hydroxyl value of at least 195. Preferably the monoglyceride content is at least 50% by weight of the total weight of the ester. Particular examples of such esters are those marketed under the trade names Dur EM® and Monomuls®.

35 Dur EM® is a mixture of α - and β -monostearates and diglycerides; the α -monostearate being present as approximately 52% by weight of the ester.

Monomuls® is a mixture containing approximately 57-62% glyceryl monostearate.

40 Examples of glycerol esters in category b) include substantially pure glyceryl distearate and examples of glycerol esters in category c) are those sold under the trademark Witepsol® as Witepsol® H 15, Witepsol® H 19 and Witepsol® W 45. The aforementioned Witepsols have an ascending melting point in the range 33.5-35.5 and hydroxyl values of 15 (maximum), 20-30 and 40-50 respectively.

Witepsol® W 45 is composed of approximately 8% (w/w) monoglyceride, 10-12% (w/w) diglyceride, approximately 80% (w/w) triglyceride and less than 0.2% (w.w) glycerol.

Preferred glycerol esters are those selected from category a).

45 Examples of sucrose esters are mixtures of mono-, di- and tri-esters, particularly those formed from palmitic and stearic acids, for example esters formed from a 30:70 mixture of palmitic:stearic acids. Particular esters are those having a hydroxyl value of greater than 130, and melting points in the range 70-80° C, for example those sold under the trade names Crodesta® F50 and Crodesta® F160 by Croda Chemicals Ltd., Goole, North Humberside, U.K. Crodesta® F50 and F160 have melting points of 74-78° C and 70-74° C respectively and have a monoester content of 29% and 75% respectively.

50 It has also been found that by including a palatable pharmaceutically acceptable emulsifier in the granules, their dissolution rate can be increased still further without reducing palatability. Typically, the emulsifier can be present in an amount up to 200% by weight, for example 100% by weight, relative to the glycerol ester. One class of pharmaceutically acceptable emulsifiers is the lecithins.

55 Preferably the lecithin contains no unsaturated fatty acids. One such lecithin is soya lecithin, particularly soya lecithin NC 95 H which contains more than 87% phosphatidyl choline, not more than 5% lysolecithin and a fatty acid component consisting of 8-12% palmitic acid and 84-88% stearic acid.

In one preferred aspect of the invention, the granulating agent is a mixture of a glycerol ester containing at least 50% by weight of a monoglyceride and having a hydroxyl value of at least 195, and soya

phosphatide each of which is present in an amount to 20% by weight relative to the cimetidine.

Granules comprising cimetidine, an ester such as a sucrose or glycerol ester and optionally an emulsifier such as a lecithin as described hereinbefore are particularly useful in the preparation of chewable tablets, and hence chewable tablets containing such granules represent a further embodiment of this invention.

The chewable tablets of this invention contain normally at least 75 mg of cimetidine. As a maximum the tablet will not normally contain more than 800 mg of cimetidine. Preferably it contains 100 or 200 mg of cimetidine.

The tablets of the invention can also contain a hydroxide or carbonate antacid. Examples of suitable antacids include aluminium hydroxide, magnesium hydroxide, magnesium carbonate, calcium carbonate and co-dried gels for example aluminium hydroxide-magnesium carbonate co-dried gel. In practice the quantity of antacid is usually between 5 milliequivalents per tablet and 40 milliequivalents, typically approximately 15 milliequivalents.

The tablets can also contain solid diluents, for example sugars such as sucrose and lactose, and sugar alcohols such as xylitol, sorbitol and mannitol. When the solid diluent is a sugar alcohol, particularly sorbitol or mannitol, it is preferred that the cimetidine granules also contain an emulsifier such as a lecithin.

The tablets can also contain sweeteners, flavours and enhancers such as ammonium glycyrrhizinate, aspartame, sodium cyclamate and sodium saccharinate, sodium chloride, sodium glutamate and Con-tramarum; and tableting starch to enhance palatability and mouth feeling.

The tablets can also contain other standard tableting excipients for example a binder and a disintegrant.

Where the tablet contains an antacid, preferably the antacid is pre-compressed or granulated before it is mixed with the cimetidine granules.

The cimetidine granules can be prepared by adding the ester or an ester/lecithin mixture to cimetidine (which optionally has been pre-heated to a temperature slightly below the melting point of the ester) and warming the mixture, by external heating or by high speed agitation, until the ester just melts. Mixing is continued for a short period of time until the mixture just granulates. In this way, within a few minutes, coated granules substantially free of agglomerates are obtained.

The granules can also be prepared by granulation in a spray-dryer according to conventional techniques.

It is preferred that prior to granulating, 90% of the cimetidine particles have an apparent diameter of less than 70 μm .

The granules can be sieved to remove fine particles and larger particles. Preferably the granules pass through a 1 mm sieve but are retained by a 0.2 mm sieve.

The cimetidine granules and the antacid (preferably granulated) are then mixed with conventional tablet excipients as described hereinbefore and compressed into tablets using the appropriate punches and dies.

The following Examples illustrate the invention.

EXAMPLES 1-7

| Chewable Tablet Containing Cimetidine/Glycerol Ester Granules and Antacid | | | | | | | |
|---|--|-------|-------|-------|-------|-------|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5 | Cimetidine | 100.0 | 100.0 | 200.0 | 100.0 | 100.0 | 200.0 |
| | Dur EM® | 20.0 | - | 40.0 | 20.0 | 20.0 | 40.0 |
| | Glycerol distearate (90%) | - | 20.0 | - | - | - | - |
| | Soyaphosphatide | - | - | - | 20.0 | - | 40.0 |
| | F-MA 11* | 300.0 | 300.0 | 300.0 | 300.0 | 300.0 | 300.0 |
| 10 | Mg(OH) ₂ | 200.0 | 200.0 | 200.0 | 200.0 | 200.0 | 200.0 |
| | Mannitol | 676.5 | 676.5 | 556.5 | - | 656.5 | - |
| | Xylitol | - | - | - | 676.5 | - | - |
| | Sucrose | - | - | - | - | 556.5 | 516.5 |
| | Microcrystalline Cellulose/ Sodium | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 |
| 15 | Carboxymethyl cellulose (Avicel® RC 581) | | | | | | |
| | Glycine | 25.0 | 25.0 | 25.0 | 25.0 | 25.0 | 25.0 |
| | Sodium cyclamate | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 | 50.0 |
| | Sodium carboxymethyl cellulose | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| | Sodium chloride | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| 20 | Sodium glutamate | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| | Hydroxypropylmethyl cellulose | 25.0 | 25.0 | 25.0 | 25.0 | 25.0 | 25.0 |
| | (Methocel® E 5) | | | | | | |
| | Calcium arachinate | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 | 20.0 |
| | Aerosil® 200 | 3.0 | 3.0 | 3.0 | 2.0 | 3.0 | 3.0 |
| 25 | Flavours | 8.0 | 8.0 | 8.0 | 8.0 | 8.0 | 8.0 |

*F-MA 11 is an aluminium hydroxide-magnesium carbonate co-dried gel.

For each of the formulations, the manufacturing process is as follows:

The cimetidine, glycerol ester (or sucrose ester - see Examples 8-9) and, where appropriate, soya lecithin (soya phosphatide) are mixed in a vacuum mixer with heating in order to melt the glycerol ester. The resulting granules are sieved through a 1mm mesh sieve.

Antacid granules are prepared by pre-mixing the FMA-11, Mg(OH)₂, Avicel®, Glycine and sodium cyclamate and then adding the Blanose®, sodium chloride, aspartame, sodium glutamate and Methocel®, and water as required. The resulting granules are dried in a fluid bed drier.

The cimetidine granules are mixed with the antacid granules, the mannitol, xylitol, calcium arachinate, Aerosil® and the flavouring agent to give a mixture which is compressed into tablets in a conventional manner.

EXAMPLES 8-9

Chewable Tablet Containing Cimetidine/Sucrose Ester Granules and an Antacid

The following tablets were prepared according to the method described in Examples 1-7.

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| | 8 | 9 |
|--|-------|-------|
| Cimetidine | 100 | 200 |
| ° Crodesta® F50 | 25 | - |
| ° Crodesta® F160 | - | 50 |
| F-MA 11 | 300 | 300 |
| Mg(OH) ₂ | 200 | 200 |
| Sucrose | 671.5 | 546.5 |
| Microcrystalline cellulose/Sodium Carboxymethyl cellulose (Avicel® RC 581) | | 50 |
| Glycine | 25 | 25 |
| Sodium Cyclamate | 50 | 50 |
| Sodium Carboxymethyl cellulose | 5 | 5 |
| Sodium chloride | 12.5 | 12.5 |
| Sodium glutamate | 5 | 5 |
| Hydroxypropylmethyl cellulose (Methocel® E5) | 25 | 25 |
| Calcium arachinate | 20 | 20 |
| Aerosil® 200 | 3 | 3 |
| Flavours | 8 | 8 |

° Crodesta® F50 and F160 are mixtures of mono-, di-and tri-esters of 30:70 palmitic:stearic acid.

Dissolution of Compositions of the invention

| Example No. | Cimetidine (mg) | Glycerol Ester (Quantity - mg) | Lecithin | Sweetener | Dissolution (%) ^{*)} 15' 30' 45' 60' | Hardness (Newtons) | Weight (g) |
|-------------|-----------------|--------------------------------|----------|-----------|--|--------------------|------------|
| 1 | 100 | Dur EM® (20) | - | Mannitol | 68 88 91 97 | 49.0 | 1.498 |
| 4 | 100 | Dur EM® (20) | - | Xylitol | 48 85 90 95 | 55.0 | 1.497 |
| 5 | 100 | Dur EM® (20) | 20 | Mannitol | 74 95 96 98 | 52.0 | 1.514 |
| 6 | 200 | Dur EM® (40) | - | Sucrose | 17 39 50 61 | 56.0 | 1.503 |
| 7 | 200 | Dur EM® (40) | 40 | Sucrose | 16 28 50 50 | 57.7 | 1.499 |
| 8 | 100 | Crodesta® F50 (25) | - | Sucrose | 26 55 80 95 | 77.6 | 1.498 |
| 9 | 200 | Crodesta® F160 (50) | - | Sucrose | 25 50 65 84 | 72.0 | 1.502 |
| 10+ | 200 | Dur EM® (40) | - | Mannitol | 44 77 93 96 | 68.0 | 1.491 |
| 11** | 200 | Dur EM® (40) | - | Xylitol | 31 45 62 93 | 67.0 | 1.711 |
| 12+ | 200 | Monomuls® (40) | - | Mannitol | 63 83 94 95 | 75.7 | 1.508 |
| 13** | 200 | Monomuls® (40) | - | Xylitol | 35 70 80 86 | 56.7 | 1.465 |

^{*)} US Pharmacopoeia-Paddle Test; 900 ml H₂O, 100 rpm, 37°C, tablets coarsely crushed in mortar before testing.

+ Examples 10 and 12 have essentially the same composition as Example 3 except that in Example 12, the glycerol ester is Monomuls® rather than Dur EM®.

** Examples 11 and 13 have essentially the same composition as Example 4 except that in Example 13, Monomuls® has been substituted for Dur EM®.

Table 1

| | mg Cimetidine | Coating material | mg coating | Granulation in | Taste ° masking | T ₉₀ % Cim. ° ° [Min.] |
|----|------------------|-----------------------|---------------|----------------|--------------------|--------------------------------------|
| 5 | 100 | Precirol®* | 50 | mixer | - | >> 60 |
| | 100 | Precirol® | 100 | mixer | + | >> 60 |
| | 100 | Kollidon® 25 | 5 | mixer | - | > 60 |
| | 100 | Dur EM® | 10 | mixer | - | 20 |
| 10 | 100 | Dur EM® | 15 | mixer | ± | 15 |
| | 100 | Dur EM® | 20 | mixer | + | 30 - 40 |
| | 100 | Dur EM® | 50 | mixer | + | 30 - 40 |
| | 200 | Dur EM® | 40 | mixer | + | 30 - 40 |
| | 200 | Monomuls® | 40 | mixer | + | 30 - 40 |
| 15 | 100 | Soyaphosphat. NC 95 H | 100 | mixer | + | > 60 |
| | 100 | Dur EM®/ NC 95 H | 20 + 20 | mixer | + | 15 - 20 |
| | 100 | Dur EM® | 20 | spray dryer | - | < 15 |
| | 100 | Dur EM® | 65 | spray dryer | - | 35 - 40 |
| | 100 | Dur EM® | 100 | spray dryer | + | 40 - 45 |
| 20 | 100 | Witepsol® H 5 | 20 | mixer | - | |
| | 100 | Witepsol® W 45 | 20 | mixer | + | 30 - 35 |
| | 100 | Glycerindist. | 20 | mixer | + | 40 - 45 |
| | 100 | Crodesta® F10 | 25 | mixer | + | >> 60 |
| | 100 | Crodesta® F50 | 25 | mixer | + | 40 - 50 |
| 25 | 100 | Crodesta® F160 | 25 | mixer | + | 40 - 50 |

*Precirol has a hydroxyl value in the range 90-110 and is composed of 40% (w/w) glyceryltripalmitostearate, 45% (w/w) glyceryldipalmitostearate, 14% (w/w) glycerylmonostearate and 1% (w/w) glycerol.

° + indicates no bitter taste

± indicates some residual bitterness but still palatable

- indicates unpalatable bitterness

Results were obtained from a panel of four tasters who chewed tablets of a composition similar to those described in the Examples.

° ° T₉₀ % Cim. is the time taken for 90% of the cimetidine in the granules to dissolve under the conditions specified on pages 1243-1244 of the US Pharmacopoeia XXI.

EXAMPLES 14-15

Chewable Tablet Containing Cimetidine/Glycerol Ester Granules and Antacid

The following tablets were prepared according to the method described in Examples 1-7.

| | 14 | 15 |
|---|-------|-------|
| Cimetidine | 100.0 | 100.0 |
| Dur EM® | 20.0 | 20.0 |
| Soyaphosphatide | - | 20.0 |
| F-MA 11* | 300.0 | 300.0 |
| Mg(OH) ₂ | 200.0 | 200.0 |
| Mannitol | - | 642.5 |
| Sucrose | 670.3 | - |
| Microcrystalline Cellulose/ Sodium Carboxymethyl cellulose (Avicel® RC 581) | 50.0 | 50.0 |
| Glycine | 25.0 | 25.0 |
| Sodium cyclamate | 50.0 | 50.0 |
| Sodium carboxymethyl cellulose (Blanose® 7 HF) | 5.0 | 5.0 |
| Sodium chloride | 12.5 | 12.5 |
| Sodium glutamate | 5.0 | 5.0 |
| Hydroxypropylmethyl cellulose (Methocel® E 5) | 25.0 | 25.0 |
| Calcium arachinate | 30.0 | 20.0 |
| Aerosil® 200 | 3.0 | 3.0 |
| Flavours | 4.2 | 25.0 |

*F-MA 11 is an aluminium hydroxide-magnesium carbonate co-dried gel.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical granule composition comprising cimetidine and, as a granulating agent and taste-masking agent, a glycerol or sucrose ester wherein at least one hydroxy group is esterified with a C₆₋₂₄ fatty acid, and where desired a palatable pharmaceutically acceptable emulsifier wherein the ester is present in an amount corresponding to at least 15% by weight relative to the cimetidine.
2. A pharmaceutical granule composition comprising cimetidine, a glycerol or sucrose ester wherein at least one hydroxy group is esterified with a C₆₋₂₄ fatty acid, and optionally a pharmaceutically acceptable palatable emulsifier, the ester and any emulsifier being selected such that the bitter taste of cimetidine is substantially masked and such that 90% by weight of the cimetidine is releasable from the granule composition within 50 minutes as measured using the US Pharmacopoeia Paddle test (paddle speed 100 r.p.m.).
3. A pharmaceutical granule composition according to claims 1 or 2 which contains a glycerol ester in an amount corresponding to at least 15% by weight relative to the cimetidine and optionally an emulsifier; wherein the glycerol ester is selected from:
 - a) glycerol esters having a hydroxyl value of greater than 120;
 - b) glycerol esters having a hydroxyl value of greater than 60 and having less than 30% by weight triglyceride content; and
 - c) glycerol esters having a hydroxyl value of greater than 5 and a melting point of less than 40 °C.
4. A composition according to claim 3 wherein the glycerol ester is present in an amount from 15% w/w to 100% w/w relative to the cimetidine.
5. A composition according to claim 4 wherein the amount of glycerol ester present is 20% w/w relative to the cimetidine.
6. A composition according to any one of claims 3 to 5 wherein the glycerol ester has a hydroxyl value of greater than 120.
7. A composition according to any one of claims 3 to 6 wherein the glycerol ester is composed of more than 50% by weight of glyceryl monostearate.

8. A composition according to any one of claims 1 to 7 containing a palatable pharmaceutically acceptable emulsifier.
9. A composition according to claim 8 wherein the emulsifier is a lecithin.
10. A composition according to claim 9 wherein the ester is a glycerol ester and the lecithin is present in an amount of up to 200% w/w, for example 100% w/w, relative to the glycerol ester.
11. A pharmaceutical granule composition according to claims 1 or 2 which contains a sucrose ester which is a mixture of mono-, di- and tri-esters with palmitic and stearic acids, the mixture having a hydroxyl value of greater than 130.
12. A chewable tablet containing a granule composition as defined in any one of claims 1 to 11.

Claims for the following Contracting States : ES, GR

1. A process for preparing a pharmaceutical granule composition comprising cimetidine and, as a granulating agent and taste-masking agent, a glycerol or sucrose ester wherein at least one hydroxy group is esterified with a C₆₋₂₄ fatty acid, and where desired a palatable pharmaceutically acceptable emulsifier, wherein the ester is present in an amount corresponding to at least 15% by weight relative to the cimetidine; which process comprises granulating the cimetidine with the ester.
2. A process for preparing a pharmaceutical granule composition comprising cimetidine, a glycerol or sucrose ester wherein at least one hydroxy group is esterified with a C₆₋₂₄ fatty acid, and optionally a pharmaceutically acceptable palatable emulsifier, the ester and any emulsifier being selected such that the bitter taste of cimetidine is substantially masked and such that 90% by weight of the cimetidine is releasable from the granule composition within 50 minutes as measured using the US Pharmacopoeia Paddle test (paddle speed 100 r.p.m.); which process comprises granulating the cimetidine with the ester.
3. A process according to either claim 1 or claim 2 which comprises adding the ester, and optionally an emulsifier, to cimetidine, warming the resulting mixture until the ester just melts and thereafter continuing mixing until granules are formed.
4. A process according to any one of claims 1 to 3 wherein the glycerol ester is present in an amount corresponding to at least 15% by weight relative to the cimetidine and optionally an emulsifier; wherein the glycerol ester is selected from:
 - a) glycerol esters having a hydroxyl value of greater than 120;
 - b) glycerol esters having a hydroxyl value of greater than 60 and having less than 30% by weight triglyceride content; and
 - c) glycerol esters having a hydroxyl value of greater than 5 and a melting point of less than 40 ° C.
5. A process according to claim 4 wherein the glycerol ester is present in an amount from 15% w/w to 100% w/w relative to the cimetidine.
6. A process according to claim 5 wherein the amount of glycerol ester present is 20% w/w relative to the cimetidine.
7. A process according to any one of claims 4 to 6 wherein the the glycerol ester has a hydroxyl value of greater than 120.
8. A process according to any one of claims 4 to 7 wherein the glycerol ester is composed of more than 50% by weight of glyceryl monostearate.
9. A process according to any one of claims 1 to 8 which comprises granulating with the cimetidine and ester, a palatable pharmaceutically acceptable emulsifier.
10. A process according to claim 9 wherein the emulsifier is a lecithin.

11. A process according to claim 10 wherein the lecithin is present in an amount of up to 200% w/w, for example 100% w/w, relative to the ester.

12. A process according to any one of claims 1 to 3 wherein the ester is a sucrose ester which is a mixture of mono-, di- and tri-esters with palmitic and stearic acids, the mixture having a hydroxyl value of greater than 130.

13. A process for preparing a chewable tablet composition which comprises forming granules according to a process as defined in any one of claims 1 to 12 and then compressing the granules, and optionally an antacid and any other excipients, to form a tablet.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique en granules comprenant de la cimétidine et, comme agent de granulation et agent de masquage du goût, un ester de glycérol ou de saccharose dans lequel au moins un groupe hydroxyle est estérifié par un acide gras en C₆-C₂₄ et, lorsque cela est souhaité, un émulsionnant de goût acceptable et pharmaceutiquement acceptable, dans laquelle l'ester est présent en une quantité correspondant à au moins 15 % en poids par rapport à la cimétidine.

2. Composition pharmaceutique en granules comprenant de la cimétidine, un ester de glycérol ou de saccharose dans lequel au moins un groupe hydroxyle est estérifié par un acide gras en C₆-C₂₄ et, facultativement, un émulsionnant de goût acceptable et pharmaceutiquement acceptable, l'ester et tout émulsionnant étant choisis de telle manière que le goût amer de la cimétidine soit sensiblement masqué et qu'une proportion de 90 % en poids de la cimétidine soit libérable de la composition du granule en moins de 50 minutes, comme mesuré par l'essai à la palette de la Pharmacopée des E.U.A. (vitesse de la palette de 100 tr/min).

3. Composition pharmaceutique en granules selon la revendication 1 ou 2, qui contient un ester de glycérol en une quantité correspondant à au moins 15 % en poids par rapport à la cimétidine et, facultativement, un émulsionnant ; dans laquelle l'ester de glycérol est choisi parmi :

- a) les esters de glycérol ayant un indice d'hydroxyle supérieur à 120 ;
- b) les esters de glycérol ayant un indice d'hydroxyle supérieur à 60 et ayant une teneur en triglycérides inférieure à 30 % en poids ; et
- c) les esters de glycérol ayant un indice d'hydroxyle supérieur à 5 et un point de fusion inférieur à 40 °C.

4. Composition selon la revendication 3, dans laquelle l'ester de glycérol est présent en une quantité de 15 % en poids à 100 % en poids par rapport à la cimétidine.

5. Composition selon la revendication 4, dans laquelle la quantité d'ester de glycérol présent est de 20 % en poids par rapport à la cimétidine.

6. Composition selon l'une quelconque des revendications 3 à 5, dans laquelle l'ester de glycérol a un indice d'hydroxyle supérieur à 120.

7. Composition selon l'une quelconque des revendications 3 à 6, dans laquelle l'ester de glycérol est composé de plus de 50 % en poids de monostéarate de glycéryle.

8. Composition selon l'une quelconque des revendications 1 à 7, contenant un émulsionnant de goût acceptable et pharmaceutiquement acceptable.

9. Composition selon la revendication 8, dans laquelle l'émulsionnant est une lécithine.

10. Composition selon la revendication 9, dans laquelle l'ester est un ester de glycérol et la lécithine est présente en une quantité d'au plus 200 % en poids, par exemple de 100 % en poids, par rapport à l'ester de glycérol.

11. Composition pharmaceutique en granules selon la revendication 1 ou 2, qui contient un ester de saccharose qui est un mélange de mono-, di- et triesters formés avec les acides palmitique et stéarique, le mélange ayant un indice d'hydroxyle supérieur à 130.

5 12. Comprimé à croquer contenant une composition en granules telle que définie dans l'une quelconque des revendications 1 à 11.

Revendications pour les Etats contractants suivants : ES, GR

10 1. Procédé pour préparer une composition pharmaceutique en granules comprenant de la cimétidine et, comme agent de granulation et agent de masquage du goût, un ester de glycérol ou de saccharose dans lequel au moins un groupe hydroxyle est estérifié par un acide gras en C₆-C₂₄ et, lorsque cela est souhaité, un émulsionnant de goût acceptable et pharmaceutiquement acceptable, dans laquelle l'ester est présent en une quantité correspondant à au moins 15 % en poids par rapport à la
15 cimétidine, lequel procédé consiste à granuler la cimétidine avec l'ester.

2. Procédé pour préparer une composition pharmaceutique en granules comprenant de la cimétidine, un ester de glycérol ou de saccharose dans lequel au moins un groupe hydroxyle est estérifié par un acide gras en C₆-C₂₄ et, facultativement, un émulsionnant de goût acceptable et pharmaceutiquement acceptable, l'ester et tout émulsionnant étant choisis de telle manière que le goût amer de la cimétidine soit sensiblement masqué et qu'une proportion de 90 % en poids de la cimétidine soit libérable de la composition du granule en moins de 50 minutes, comme mesuré par l'essai à la palette de la Pharmacopée des E.U.A. (vitesse de la palette de 100 tr/min), lequel procédé consiste à granuler la
20 cimétidine avec l'ester.

25 3. Procédé selon l'une ou l'autre des revendications 1 et 2, qui consiste à ajouter l'ester, et facultativement un émulsionnant, à la cimétidine, chauffer le mélange résultant jusqu'à ce que l'ester commence à fondre, puis continuer à mélanger jusqu'à ce que les granules soient formés.

30 4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel l'ester de glycérol est présent en une quantité correspondant à au moins 15 % en poids par rapport à la cimétidine et un émulsionnant est facultativement présent, dans lequel l'ester de glycérol est choisi parmi :

- a) les esters de glycérol ayant un indice d'hydroxyle supérieur à 120 ;
 - b) les esters de glycérol ayant un indice d'hydroxyle supérieur à 60 et ayant une teneur en triglycérides inférieure à 30 % en poids ; et
 - c) les esters de glycérol ayant un indice d'hydroxyle supérieur à 5 et un point de fusion inférieur à 40 ° C.
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40 5. Procédé selon la revendication 4, dans lequel l'ester de glycérol est présent en une quantité de 15 % en poids à 100 % en poids par rapport à la cimétidine.

6. Procédé selon la revendication 5, dans lequel la quantité d'ester de glycérol est de 20 % en poids par rapport à la cimétidine:

45 7. Procédé selon l'une quelconque des revendications 4 à 6, dans lequel l'ester de glycérol a un indice d'hydroxyle supérieur à 120.

8. Procédé selon l'une quelconque des revendications 4 à 7, dans lequel l'ester de glycérol est composé de plus de 50 % en poids de monostéarate de glycéryle.

50 9. Procédé selon l'une quelconque des revendications 1 à 8, qui consiste à granuler avec la cimétidine et l'ester un émulsionnant de goût acceptable et pharmaceutiquement acceptable.

10. Procédé selon la revendication 9, dans lequel l'émulsionnant est une lécithine.

55 11. Procédé selon la revendication 10, dans lequel la lécithine est présente en une quantité d'au plus 200 % en poids, par exemple de 100 % en poids, par rapport à l'ester.

12. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel l'ester est un ester de saccharose qui est un mélange de mono-, di- et triesters formés avec les acides palmitique et stéarique, le mélange ayant un indice d'hydroxyle supérieur à 130.

5 13. Procédé pour préparer une composition de comprimé à croquer, qui consiste à former des granules selon un procédé tel que défini dans l'une quelconque des revendications 1 à 12, puis à presser les granules, avec facultativement un antiacide et divers autres excipients, pour former un comprimé.

Patentansprüche

10 Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Arzneimittel in Granulatform, umfassend Cimetidin und als Granulierungs- und Geschmacksmaskierungsmittel, einen Glycerin- oder Sucroseester, in dem mindestens eine Hydroxylgruppe mit einer C₆₋₂₄-Fettsäure verestert ist und gewünschtenfalls ein wohlschmeckendes pharmazeutisch verträgliches Emulgiermittel, wobei der Ester in einer Menge vorliegt, die mindestens 15 Gew.-%, bezogen auf das Cimetidin, entspricht.

2. Arzneimittel in Granulatform, umfassend Cimetidin, einen Glycerin- oder Sucroseester, in dem mindestens eine Hydroxylgruppe mit einer C₆₋₂₄-Fettsäure verestert ist und gegebenenfalls ein wohlschmeckendes pharmazeutisch verträgliches Emulgiermittel, wobei der Ester und jegliches Emulgiermittel so gewählt ist, daß der bittere Geschmack des Cimetidins im wesentlichen überdeckt ist und daß 90 Gew.-% des Cimetidins vorliegt aus der Granulatzusammensetzung innerhalb von 50 Minuten freisetzbar ist, gemessen unter Verwendung des US Pharmacopoeia Paddle-Tests (Paddle-Geschwindigkeit 100 U.p.M.).

3. Arzneimittel in Granulatform nach den Ansprüchen 1 oder 2, enthaltend einen Glycerinester in einer Menge entsprechend mindestens 15 Gew.-%, bezogen auf das Cimetidin, und gegebenenfalls ein Emulgiermittel, wobei der Glycerinester ausgewählt ist aus:
(a) Glycerinestern mit einem Hydroxylwert von mehr als 120;
(b) Glycerinestern mit einem Hydroxylwert von mehr als 60 und weniger als 30 Gew.-% Triglyceridgehalt; und
(c) Glycerinestern mit einem Hydroxylwert von mehr als 5 und einem Schmelzpunkt von weniger als 40 °C.

4. Mittel nach Anspruch 3, in dem der Glycerinester in einer Menge von 15 Gew.-% bis 100 Gew.-%, bezogen auf das Cimetidin, vorliegt.

5. Mittel nach Anspruch 4, in dem die Menge des vorhandenen Glycerinesters 20 Gew.-%, bezogen auf das Cimetidin, beträgt.

6. Mittel nach einem der Ansprüche 3 bis 5, in dem der Glycerinester einen Hydroxylwert von mehr als 120 aufweist.

7. Mittel nach einem der Ansprüche 3 bis 6, in dem der Glycerinester aus mehr als 50 Gew.-% Glycerinmonostearat besteht.

8. Mittel nach einem der Ansprüche 1 bis 7, enthaltend ein wohlschmeckendes pharmazeutisch verträgliches Emulgiermittel.

9. Mittel nach Anspruch 8, in dem das Emulgiermittel ein Lecithin ist.

10. Mittel nach Anspruch 9, in dem der Ester ein Glycerinester ist und das Lecithin in einer Menge von bis zu 200 Gew.-%, beispielsweise 100 Gew.-%, bezogen auf den Glycerinester, vorliegt.

11. Arzneimittel in Granulatform nach den Ansprüchen 1 oder 2, enthaltend einen Sucroseester, der ein Gemisch von Mono-, Di- und Triester mit Palmitin- und Stearinsäure ist, wobei das Gemisch einen Hydroxylwert von mehr als 130 aufweist.

12. Eine kaubare Tablette, enthaltend ein Mittel in Granulatform nach einem der Ansprüche 1 bis 11.

Patentansprüche für folgende Vertragsstaaten : ES, GR

- 5 1. Verfahren zur Herstellung eines Arzneimittels in Granulatform, umfassend Cimetidin und als Granulierungs- und Geschmacksmaskierungsmittel einen Glycerin- oder Sucroseester, in dem mindestens eine Hydroxylgruppe mit einer C₆₋₂₄-Fettsäure verestert ist und gewünschtenfalls ein wohlschmeckendes pharmazeutisch verträgliches Emulgiermittel, wobei der Ester in einer Menge vorliegt, die mindestens 15 Gew.-%, bezogen auf das Cimetidin, entspricht, wobei das Verfahren das Granulieren des Cimetidins mit dem Ester umfaßt.
- 10 2. Verfahren zur Herstellung eines Arzneimittels in Granulatform, umfassend Cimetidin, einen Glycerin- oder Sucroseester, in dem mindestens eine Hydroxylgruppe mit einer C₆₋₂₄-Fettsäure verestert ist und gegebenenfalls ein wohlschmeckendes, pharmazeutisch verträgliches Emulgiermittel, wobei der Ester und jegliches Emulgiermittel so gewählt ist, daß der bittere Geschmack des Cimetidins im wesentlichen überdeckt ist und daß 90 Gew.-% des Cimetidins aus der Granulat-Zusammensetzung innerhalb von 50 Minuten freisetzbar ist, gemessen unter Verwendung des US-Pharmacopoeia Paddle-Test (Paddle-Geschwindigkeit 100 U.p.M.), wobei das Verfahren das Granulieren des Cimetidins mit dem Ester umfaßt.
- 15 3. Verfahren nach einem der Ansprüche 1 oder 2, umfassend die Zugabe des Esters, und gegebenenfalls eines Emulgiermittels, zu dem Cimetidin, Erwärmen des erhaltenen Gemisches bis der Ester gerade schmilzt und anschließend weiteres Mischen bis sich das Granulat bildet.
- 20 4. Verfahren nach einem der Ansprüche 1 bis 3, wobei der Glycerinester in einer Menge entsprechend mindestens 15 Gew.-%, bezogen auf das Cimetidin und gegebenenfalls das Emulgiermittel vorliegt, wobei der Glycerinester ausgewählt ist aus:
 - (a) Glycerinestern mit einem Hydroxylwert von mehr als 120;
 - (b) Glycerinestern mit einem Hydroxylwert von mehr als 60 und weniger als 30 Gew.-% Triglyceridgehalt; und
 - (c) Glycerinestern mit einem Hydroxylwert von mehr als 5 und einem Schmelzpunkt von weniger als 40 °C.
- 25 5. Verfahren nach Anspruch 4, bei dem der Glycerinester in einer Menge von 15 Gew.-% bis 100 Gew.-%, bezogen auf das Cimetidin, vorliegt.
- 30 6. Verfahren nach Anspruch 5, in dem die Menge des vorhandenen Glycerinesters 20 Gew.-%, bezogen auf das Cimetidin, beträgt.
- 35 7. Verfahren nach einem der Ansprüche 4 bis 6, in dem der Glycerinester einen Hydroxylwert von mehr als 120 aufweist.
- 40 8. Verfahren nach einem der Ansprüche 4 bis 7, in dem der Glycerinester aus mehr als 50 Gew.-% Glycerylmonostearat besteht.
- 45 9. Verfahren nach einem der Ansprüche 1 bis 8, umfassend das Granulieren eines wohlschmeckenden, pharmazeutisch verträglichen Emulgiermittels mit dem Cimetidin und dem Ester.
- 50 10. Verfahren nach Anspruch 9, wobei das Emulgiermittel ein Lecithin ist.
- 55 11. Verfahren nach Anspruch 10, wobei das Lecithin in einer Menge von bis zu 200 Gew.-%, beispielsweise 100 Gew.-%, bezogen auf den Ester, vorliegt.
12. Verfahren nach einem der Ansprüche 1 bis 3, wobei der Ester ein Sucroseester ist, der ein Gemisch von Mono-, Di- und Triester mit Palmitin- und Stearinsäure darstellt, wobei das Gemisch einen Hydroxylwert von mehr als 130 aufweist.
13. Verfahren zur Herstellung eines Mittels in Form einer kaubaren Tablette, umfassend die Erzeugung von

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Granulat nach einem in einem der Ansprüche 1 bis 12 beschriebenen Verfahren und anschließend Verpressen des Granulats und gegebenenfalls eines Antiazidikums und irgendwelcher anderer Trägerstoffe zur Erzeugung einer Tablette.

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